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ABSTRACT

This monograph examines the effectiveness of adjuvant chemotherapy in premenopausal women with breast cancer that has spread to the lymph nodes under the arm. The review focuses on the issue of how the survival of node-positive breast cancer patients has changed over time. It concludes that the survivability benefits from this treatment need further study since no visible improvement was indicated in the findings. (JD)

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United States General Accounting Office

GAO

Report to the Chairman, Subcommittee on Health and the Environment, Committee on Energy and Commerce, House of Representatives

February 1989

BREAST CANCER

Patients' Survival

GP031 181

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Program Evaluation and
Methodology Division

B-226468

February 28, 1989

The Honorable Henry A. Waxman
Chairman, Subcommittee on Health and
the Environment
Committee on Energy and Commerce
House of Representatives

Dear Mr. Chairman:

In your June 2, 1987, letter, you asked us to examine several issues related to the application of cancer treatments. This report is the third and final in a series of reports prepared in response to your request. In earlier reports to you in January 1988 and October 1988, we discussed the extent to which cancer patients actually receive state-of-the-art therapies and the role played by the National Cancer Institute in encouraging physicians to adopt advances in cancer treatment.

This report discusses the extent to which one advance in the treatment of breast cancer has benefited patients. It specifically examines how the survival of breast cancer patients has changed since the introduction of adjuvant chemotherapy.

As we arranged with your office, unless you publicly announce the contents of this report earlier, we plan no further distribution of it until 30 days from the date of the report. At that time, copies will be sent to the Department of Health and Human Services. We will also make copies available to interested organizations, as appropriate, and to others upon request. For further information, please call me (275-1854) or Michael J. Wargo, my associate director (275-3092).

Major contributors to this report are listed in appendix IV.

Sincerely yours,

Eleanor Chelimsky
Assistant Comptroller General

Executive Summary

Purpose

As a nation, we continue to spend billions of dollars to discover, develop, test, and refine new medical technologies. However, little effort is exerted to determine if these technologies, once they are ready for public use, realize the potential they displayed during their development. The purpose of this report is to examine the extent to which one advance in the treatment of breast cancer has benefited patients. This report responds to a request by the Subcommittee on Health and the Environment of the House Committee on Energy and Commerce that GAO examine the issue of cancer patient care.

Background

In the mid-1970's, great excitement was generated by reports from two separate clinical trials that chemotherapy administered following surgery (adjuvant chemotherapy) was beneficial for premenopausal women with breast cancer that had spread to the lymph nodes under the arm. Subsequent to these reports, the use of adjuvant chemotherapy increased considerably for this group of patients.

The results of continued experimentation on the benefits of adjuvant chemotherapy led to a consensus that "adjuvant chemotherapy has demonstrated a significant reduction in mortality in premenopausal women with histologically positive axillary lymph nodes." In light of this consensus that adjuvant chemotherapy can increase survival, and given the increased use of this therapy, logic would indicate that the survival of premenopausal, node-positive breast cancer patients should have improved since the introduction of adjuvant chemotherapy. The issue of how the survival of breast cancer patients has changed over time is the focus of this review.

Results in Brief

Despite a considerable increase in the use of chemotherapy since 1975, there has been no detectable increase in survival for the patients who should have benefited most from the advent of this therapy. Although this finding could be interpreted as evidence that chemotherapy is not beneficial, such an interpretation is unlikely to be correct. Controlled, prospectively designed, clinical studies have been conducted and have shown that chemotherapy does extend survival for specific types of breast cancer patients. When these studies were critically examined by cancer experts around the world, a consensus was reached that adjuvant chemotherapy improves the survival of premenopausal, node-positive breast cancer patients. GAO's work does not contradict these findings. What it does show is that there seem to have been problems in moving the treatment for breast cancer from the laboratory to the

patients. GAO believes that the issue of the survivability benefits from postsurgery chemotherapy treatments needs further study.

Principal Findings

The accompanying table shows the treatment and survival patterns for the group of patients who should have benefited most from adjuvant chemotherapy.

Table 1: Premenopausal, Node-Positive, Stage II Breast Cancer Patients: Treatment and Survival Patterns

Year of diagnosis	Percent receiving chemotherapy	Survival rate[a]		
		3-year	5-year	7-year
1975	23%	.82	.72	.64
1976	45	.85	.71	.64
1977	46	.83	.71	.64
1978	53	.83	.70	.63
1979	55	.83	.71	.65
1980	62	.86	.77	
1981	66	.83	.72	
1982	72	.84		
1983	69	.85		

[a]The survival rates provided assume complete follow-up only through the end of 1985. That is why the last year for 3-year survival is 1983, for 5-year, 1981, and for 7-year, 1979.

When these data are subjected to statistical tests, they show no statistically significant improvement in patients' survival. This finding was consistent across all three analytic methods GAO employed to detect changes in survival. GAO concludes that the lack of a detectable improvement in patients' survival may result from one or a combination of the following:

- Many patients still do not receive adjuvant chemotherapy.
- The benefits of chemotherapy are small and therefore difficult to detect.
- There are problems with how well the treatments are implemented.

One additional finding was that the survival of women diagnosed in 1980 was greater than that of women diagnosed in any other year. GAO could find no explanation for this finding.

Recommendation

GAO recommends that the secretary of the Department of Health and Human Services (HHS) initiate a study to determine why there has been no visible improvement in the survival of premenopausal, node-positive breast cancer patients despite the advent of adjuvant chemotherapy. Given the methodological obstacles involved in such a study, the secretary should seek expert advice in assessing the feasibility of conducting the recommended research and in developing the study design most likely to succeed. (See pp. 26-27.)

Agency Comments

In HHS's response to a draft of this report, it concurred with GAO's recommendation, suggesting a small modification with which GAO concurs. The recommendation as stated above incorporates HHS's views.

The most pervasive concern expressed by HHS in its written comments was that the study design GAO used had low statistical power. HHS pointed out that this is the case because the maximum benefit that can be derived from adjuvant chemotherapy is "modest," ranging from 7.3 to 10.8 percentage points. However, GAO's study was begun on the basis of HHS's response to a 1987 GAO report in which HHS argued that there was a "confirmed 25 percent improved survival for Stage II premenopausal women treated with adjuvant chemotherapy." If this 25-percent figure is used, the power of GAO's study is adequate.

The fact that HHS has presented conflicting estimates of the expected benefits of adjuvant chemotherapy suggests the need for further study of what has happened in the treatment of breast cancer patients. Further bolstering GAO's recommendation is HHS's agreement that large numbers of patients still do not receive adjuvant chemotherapy and that problems with how well the treatments are implemented may contribute to the absence of a detectable improvement in survival among premenopausal Stage II breast cancer patients.

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Abbreviations

CMF	Cyclophosphamide, methotrexate, and 5-fluorouracil
HHS	Department of Health and Human Services
L-PAM	L-phenylalanine mustard
NCI	National Cancer Institute
NSABP	National Surgical Adjuvant Breast Project
SEER	Surveillance, Epidemiology, and End Results

Adjuvant Chemotherapy and Breast Cancer

Introduction

Whether a new treatment has the potential to benefit patients is a question that is best answered under controlled, experimental conditions. An equally important question, and one that cannot be answered through experiments, is whether the treatment actually benefits patients in the "real world" once the experiments have been concluded. Our objective in this report is to determine, for one specific medical advance, whether its potential to extend patient survival has been realized.

This report responds to a request from the Subcommittee on Health and the Environment of the House Committee on Energy and Commerce that we examine the issue of cancer patient care. The specific focus of our work is on the advance made when it was discovered that administering chemotherapy following surgery (adjuvant chemotherapy) improves the survival chances of premenopausal breast cancer patients. In the remainder of this chapter, we give a brief historical overview of this discovery.

The Development of Adjuvant Chemotherapy

Until the 1960's, the only two options available for effectively treating most forms of cancer were surgery and radiation therapy. The benefits and limitations of surgery were clear-cut. If the operation could remove all the cancerous cells from the body, the patient was often cured. If not, the patient invariably died. Although radiation therapy expanded the physician's ability to reach and kill cancer cells, it too had the same basic limitation as surgery. That is, both treatments were effective only for achieving local control. Once cancer cells had spread through the body by the process of metastasis, neither surgery nor radiation therapy could offer much hope of cure.

All this changed with the introduction of chemotherapy to the armamentarium of cancer care. Chemotherapy—that is, treatments that use drugs to "poison" cancer cells—allowed cancer to be treated for the first time as a systemic disease. Using drugs that spread throughout the body, cancerous deposits could be attacked wherever they were located.

Although it was known in the 1920's that certain drugs could kill cancer cells, it was not until the late 1950's that researchers were able to develop a practical treatment for one relatively rare form of cancer. This was followed by the determination in the mid-1960's that a combination of drugs could be successfully used to treat acute lymphocytic leukemia, the most common form of childhood leukemia. Since then, different combinations of chemotherapy have been shown to work against many other forms of cancer.

For the most part, however, until the mid-1970's, drugs showed little promise in treating carcinomas, the "solid tumors" that account for approximately 85 percent of all cancer cases in this country. Then there was some promising news. Two articles appeared within a year of each other, describing the results of experiments on the use of adjuvant chemotherapy to treat breast cancer patients. The first of the articles, in 1975, was from the National Surgical Adjuvant Breast Project (NSABP) study that compared surgery patients receiving L-phenylalanine mustard (L-PAM) after their operations to patients receiving no additional therapy after surgery.[1] Preliminary results from this trial showed that patients treated with L-PAM had longer "disease-free survival" than their counterparts, who had only surgery as treatment.[2] Little more than a year later, even more exciting news came from an experiment conducted in Italy. Researchers at the Milan Tumor Institute reported that breast cancer patients treated with a combination of three drugs following surgery (cyclophosphamide, methotrexate, and 5-fluorouracil, or CMF) had one fourth the recurrence rate that women had whose treatment included only surgery.[3]

The immediate reaction to the article describing the Italian study was considerable. In an editorial appearing in the same journal issue, the work was described as being of "monumental importance" and the findings were characterized as "nothing short of spectacular."[4] More importantly, the percentage of premenopausal, node-positive patients receiving chemotherapy almost doubled in 1976 and continued to rise until 1982. No doubt much of this positive reaction stemmed from the fact that chemotherapy had been finally shown to have some effect, in a clinical setting, against a prevalent form of cancer.

What was perhaps missed in the initial assessment of the adjuvant therapy trials was that the results were based on a very short observation period. In fact, the length of follow-up in the Italian study was so short that the researchers who reported the results warned that their "results should be considered with caution, the effect on survival not being

[1]B. Fisher et al., "L-Phenylalanine Mustard (L-PAM) in the Management of Primary Breast Cancer: A Report of Early Findings," New England Journal of Medicine, 292:3 (1975), 117-22.

[2]"Disease-free survival" is defined as the length of time that passes between the date of diagnosis and either recurrence or the end of an observation period.

[3]G. Bonadonna et al., "Combination Chemotherapy as an Adjuvant Treatment in Operable Breast Cancer," New England Journal of Medicine, 294:8 (1976), 405-10.

[4]J.F. Holland, "Major Advance in Breast Cancer Therapy," New England Journal of Medicine, 294:8 (1976), 440-41.

known." This warning turned out to be prophetic. Once a sufficiently long period had passed in which to evaluate the benefits of chemotherapy on extending overall survival (as opposed to reducing recurrences), the results in both the Milan and NSABP studies were found to be less dramatic. The "final" results showed a benefit for chemotherapy among all premenopausal, node-positive patients in the Milan trial and a more limited benefit in the NSABP study (only premenopausal patients with fewer than four positive nodes).

As patients were observed for longer periods of time, the shifting results of adjuvant chemotherapy trials led to both debate on the efficacy of drugs for treating breast cancer and further experimentation.[5] The NSABP continued in its plans to add other drugs to L-PAM to see if combinations of drugs would be more effective than single agents.[6] The researchers in Milan compared different durations of therapy (6 versus 12 cycles) to one another.[7] New drugs were tried, as were combinations of drugs with established or new modalities of treatment.[8] Research was conducted both here and abroad.[9]

In response to the growing body of knowledge developed from these trials, the National Institutes of Health convened experts from around the world to see if there was agreement on the benefits of chemotherapy. At this 1985 meeting, a consensus was reached that

"adjuvant chemotherapy has demonstrated a highly significant increase in disease-free survival and a significant reduction in mortality in premenopausal women with

[5]For an illustration of the debate, see S.H. Levitt and R.A. Potish, "The Case for Adjuvant CMF Chemotherapy in Breast Cancer: Has It Been Made?" Cancer Clinical Trials, 4 (1981), 363-64.

[6]B. Fisher et al., "Adjuvant Chemotherapy for Breast Cancer: An Overview of NSABP Findings," International Advances in Surgical Oncology, vol. 5 (New York: Alan R. Liss, Inc., 1982), pp. 65-90.

[7]G. Bonadonna et al., "Adjuvant Chemotherapy Trials in Resectable Breast Cancer with Positive Axillary Lymph Nodes: The Experience of the Milan Cancer Institute," in S.E. Jones and S.E. Salmon (eds.), Adjuvant Therapy of Cancer IV (Orlando, Fla.: Grune & Stratton, 1984), pp. 195-207.

[8]J.M. Morrison et al., "The West Midlands Trial of Adjuvant Chemotherapy for Axillary Node Positive Breast Cancer: A Controlled Clinical Trial," in Jones and Salmon, pp. 253-59; D.C. Smith et al., "Adjuvant Radiotherapy Chemotherapy in Breast Cancer," in Jones and Salmon, pp. 283-89; T.B. Hakes et al., "CMF +/− Levamisole Breast Adjuvant Chemotherapy: 5-year Analysis," Proceedings of the American Society of Clinical Oncology, 1:83 (1982).

[9]The NSABP studies are one example of U.S. research. The West Midlands trial was conducted in England and the original CMF trial in Italy, to name but two of the foreign studies.

histologically positive axillary lymph nodes. Adjuvant chemotherapy can now be considered standard care for these patients."[11]

This consensus statement shows that the question of whether chemotherapy has the potential to extend patient survival has been settled. What has not yet been resolved is whether the actual use of chemotherapy has realized this potential.

Report Overview

In the next chapter, we describe how our study was conducted. In that context, we describe the data we used, why we focused on adjuvant chemotherapy for breast cancer, how patients were selected for inclusion in the study, how "benefit" is defined, and the analyses that were performed to develop and support our findings. Our results are presented in chapter 3, the concluding chapter of the report. A discussion of statistical issues is provided in appendix I and the patient selection criteria are described in appendix II. The comments of the Department of Health and Human Services (HHS) are in appendix III. Appendix IV lists the major contributors to this report.

[11] National Institutes of Health, Consensus Development Conference Statement, Adjuvant Chemotherapy for Breast Cancer, 5:12 (1985).

Chapter 2

Objective, Scope, and Methodology

The objective of this study is to determine whether there has been any detectable change in survival for the group of breast cancer patients who should have benefited the most from the increasing use of adjuvant chemotherapy. The scope of the project was largely defined by the availability of data, the advances in treatment that have been made in recent decades, and the population of patients for whom those advances were relevant. Each of these dimensions is discussed below, followed by descriptions of how "benefits" are measured and how the analyses that support our findings were conducted.

Data Source: The SEER Program

Given our objective of determining whether there was any change in survival for a specific group of patients, we needed a data set that contained information on the characteristics of both the disease and patients and that tracked patients over time. The Surveillance, Epidemiology, and End Results (SEER) program, initiated by the National Cancer Institute (NCI) in 1972 and currently the primary source for data on cancer incidence and patient survival, provided us with the needed data.

Twice a year, SEER receives information on incidence and follow-up for cancer patients from population-based cancer registries in the United States and Puerto Rico. Together, these registries cover 12 percent of the total population. The population covered by SEER is not a probability sample of the country, but the data are believed to represent overall cancer patterns.

The SEER data base contains information at the case level on the type of cancer, the date of diagnosis, how far the disease had advanced when it was discovered, how the patient was treated, the most recent date that contact was made with the patient, and whether the patient was alive or dead on that date. In addition, SEER also provides information on patients' characteristics (age, race, and sex) that is useful for creating homogeneous strata of patients for analysis.

When we began our study, the last full annual cohort of patients in SEER were those who were diagnosed during 1985. For this reason, we used that year as the cutoff for entering patients into our study. Our decision to restrict entry at the other end to patients diagnosed after 1974 was based on the fact that the treatment advance (adjuvant chemotherapy) was made in 1975. Since follow-up data for patients were available only through 1986, this meant that for patients diagnosed in later years, only short-term survival could be computed (for example, only 1-year survival was available for patients diagnosed in 1985).

Criteria for Selecting Adjuvant Chemotherapy for Breast Cancer

In our earlier study, in which we examined the use of "breakthrough" treatments, we required criteria to decide which advances in treatment should be included.[1] We established three criteria:

1. the treatment had been proven to increase patients' survival in a large randomized clinical trial (necessary to ensure that benefits of the advance were measurable),

2. the results of that trial had been published by 1982 (so as to allow us to determine patterns of use with the available data on treatment), and

3. the treatment was relevant for an identifiable group of cancer patients (so that we could include in our analyses only the patients who should have benefited from treatment).

As we began our first study, we asked the assistance of NCI in determining the therapies that met all three requirements. In response to our request, NCI forwarded a list of treatments, seven of which were included in our report.[2]

In the present study, the focus is on the actual benefits of the new therapies to patients. The analyses we used to determine benefit required that three additional criteria be satisfied for any therapy to be appropriate for inclusion. One of these was that the therapy be relevant for a large enough number of patients to ensure that the estimates of benefits not be overly subject to random fluctuations as a consequence of small sample size. The second criterion was that there be no known change in the prognosis of patients that was unrelated to treatment. Any such change would make it impossible to determine why patient survival had (or had not) improved over time. The final criterion was that there be a considerable increase in the frequency with which the treatment advance was given to patients. Such an increase clearly had to have occurred before treatment-related survival gains could be expected.

[1]U.S. General Accounting Office, Cancer Treatment 1975-85: The Use of Breakthrough Treatments for Seven Types of Cancer, GAO/PEMD-88-12BR (Washington, D.C.: January 1988).

[2]The seven were adjuvant chemotherapy for breast cancer and colon cancer, adjuvant radiation therapy for rectum cancer, and chemotherapy for small-cell lung cancer, testicular cancer, Hodgkin's disease, and non-Hodgkin's lymphoma.

The only therapy that met the three criteria added for this study was adjuvant chemotherapy for the treatment of premenopausal breast cancer patients.[3] No apparent change in prognostic factors for this group of patients has been noted, and, since 1975, there has been a considerable increase in the frequency with which the therapy is given.

It seemed important to examine improvements in breast cancer patients' survival for two reasons. First, the incidence of the disease is on the rise, as is the mortality rate, among premenopausal women. Second, the recent decision by NCI to issue a clinical alert recommending that adjuvant chemotherapy also be considered for all node-negative patients focused new attention on the question of the extent to which node-positive breast cancer patients have actually benefited from such therapy.

The Selection of Patients

Few if any treatments are appropriate for all patients suffering from any one type of cancer. As a disease progresses, the appropriate treatment for it typically changes. Given that our goal was to determine whether breast cancer patients benefited from the advent of adjuvant chemotherapy, it was reasonable to focus on the patients for whom the treatment had been proven effective. As mentioned above, the initial clinical trials showed chemotherapy to be effective only for premenopausal, node-positive patients. For this reason (and at the suggestion of NCI staff) we included in our analyses only breast cancer patients 50 years of age or younger at time of diagnosis (as a surrogate for menopausal status) who were node-positive and who did not have any metastases to distant sites.[4] Using these criteria, as well as a requirement that a tumor not exceed 5 centimeters in size upon diagnosis, we selected all the breast cancer patients in the SEER data base who satisfied our criteria and were diagnosed after 1974.

Measuring Benefits

Progress against disease can come in many different forms, including new or improved treatments. When a new treatment is developed, it can

[3]The treatments for prostate, colon, and rectum cancer had not been proven to extend survival in trials concluded by 1982. The treatments for osteosarcoma and soft-tissue sarcoma would not yield large enough samples of patients. The treatments for the two lymphomas and testicular cancer showed no increased use over the 11-year period for which data were available. Finally, a data problem with small-cell lung cancer made patients diagnosed after 1982 noncomparable with patients whose cancers had been detected by then. The specific problem was a change in how the extent of disease was coded in SEER data.

[4]The age cutoff of 50 is not a perfect surrogate for menopausal status because the onset of menopause may be earlier or later and some women have hysterectomies that induce early menopause.

be seen as beneficial for different reasons. For example, the treatment may increase cure rates, reduce treatment-associated side effects, reduce cost, or increase the length of time until relapse. Which of these benefits is the most "important" is impossible to say, and it is likely that the value of each one is weighed differently by patients, physicians, researchers, and health insurance providers. The benefits also differ considerably in the ease with which they can be measured. For this study, we selected overall survival as the benefit of interest.[5]

Three factors support our decision to focus on overall survival. First and foremost, whether a patient lives and, if so, for how long are clearly important considerations. Second, measuring overall survival is more feasible than measuring more abstract concepts such as "quality of life." Finally, the clinical trials that showed adjuvant chemotherapy to be beneficial for young breast cancer patients based that conclusion on the ability of chemotherapy to extend life.

Our focus on overall survival, while appropriate, also means that our conclusions on the benefits of therapy should not be extended to reach conclusions on such issues as whether breast cancer patients live healthier or happier lives than they used to.

Analysis Plan

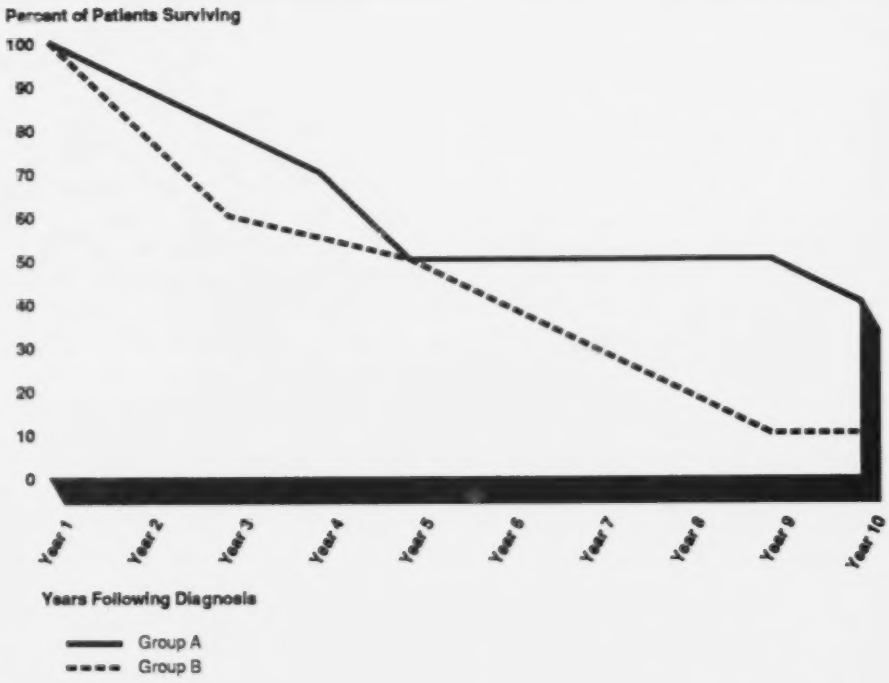
The logic underlying our analyses rests on two facts: chemotherapy has been shown to be effective in extending the lives of premenopausal, node-positive breast cancer patients, and there has been a dramatic, twofold to threefold increase in the use of chemotherapy for this class of patients in recent years.[6] From these facts, it follows that one should be able to observe some improvement in the survival experiences of breast cancer patients. To test whether this actually occurred, we employed three different statistical procedures. Each of the procedures involved making comparisons between diagnostic cohorts (that is, cohorts that are defined by the year in which the patients were diagnosed as having cancer).

[5]Overall survival is defined as the time that passes between the date of diagnosis (starting point) and either death or the end of data collection (ending point), whichever comes first.

[6]The ambiguity regarding the magnitude of the increase is a function of how one enumerates the patients for whom chemotherapy was planned but for whom SEER does not indicate whether it was given. If these patients are counted as getting chemotherapy, the threefold increase is the more accurate figure.

One approach we took was to compare observed survival rates of each successive diagnostic cohort.[7] Despite the frequency with which survival rates are used, one problem with them is that they take measurements only at specific points and not across entire intervals. Figure 2.1 shows the erroneous conclusions that can be reached by examining only survival rates.

Figure 2.1: Hypothetical Survival Curves



As can be seen from this figure, the percentage of group A that remains alive is always greater than the percentage of group B, except at the 5-year point. If we compared only 5-year survival rates, both groups would look the same, even though they have different survival profiles. Examining survival rates at more than one point (for example at 3, 5, and 7 years) reduces the likelihood of making this type of error but does not eliminate it.

[7] The observed survival rate is defined as the percentage of patients who survive for a specified period of time (for example, 5 years) from the time of diagnosis.

The second set of analyses we performed avoids the limitations of "point comparisons." In these analyses, we compared the survival experiences of women diagnosed in 1975 with those diagnosed in 1976, those diagnosed in 1976 with those diagnosed in 1977, and so on, through 1984-85, using the lifetable method.[9] This procedure compares actual length of survival (not only percentage surviving at specified times) of all cases across groups and provides statistical tests that indicate whether survival is different between the groups. We employed the LIFETEST procedure that is available on the SAS software program to perform these analyses. In evaluating the output from these computer runs, our principal focus was on the significance levels achieved in the Generalized Wilcoxon and Logrank tests.[10]

Because of the possibility that the populations we compared changed in some way and that, if such changes occurred, they might be related to survival, we also analyzed the data using a procedure known as proportional hazard modeling.[10] For this analysis, also known as Cox regression, we simultaneously entered four variables that identified the age and race of the patient, the size of the tumor, and how far the tumor had extended at the time of diagnosis, as well as 10 dummy variables denoting the year in which the cancer was diagnosed. In reviewing the results of this analysis, our focus was on whether the Beta coefficients associated with the year of diagnosis dummy variables achieved statistical significance.[11] Significant coefficients would mean that any change in the risk of dying was probably "real" (not a function of chance). If the coefficients did not achieve significance, we concluded that any observed change was probably the result of chance.

[9]Elisa T. Grant, Statistical Methods for Survival Data Analysis (Belmont, Calif.: Wadsworth, Inc., 1980), ch. 5, and David Oakes, "Survival Analysis," European Journal of Operations Research, vol. 12 (1983), 3-14.

[10]Significance level is defined as the probability that any observed difference is simply the result of chance.

[10]D.M. Finkelstein and R.A. Wolfe, "Methods of Survival Analysis," in R.G. Cornell (ed.), Statistical Methods for Cancer Studies (New York: Marcel Dekker Inc., 1984), pp. 147-52.

[11]The Beta coefficients (which actually denote a hazard function) can be transformed (by exponentiation) to provide a measure known as the relative risk. If the relative risk is greater than 1.0, then there is an increased hazard, and if less than 1.0, a decreased hazard.

Our findings also include data on patterns of use for adjuvant chemotherapy. These are drawn from our January 1988 report, to which readers are referred for a description of how that analysis was performed.[12]

Our work was performed in accordance with generally accepted government auditing standards. However, it should be noted that we did not verify the SEER data provided to us by NCI.

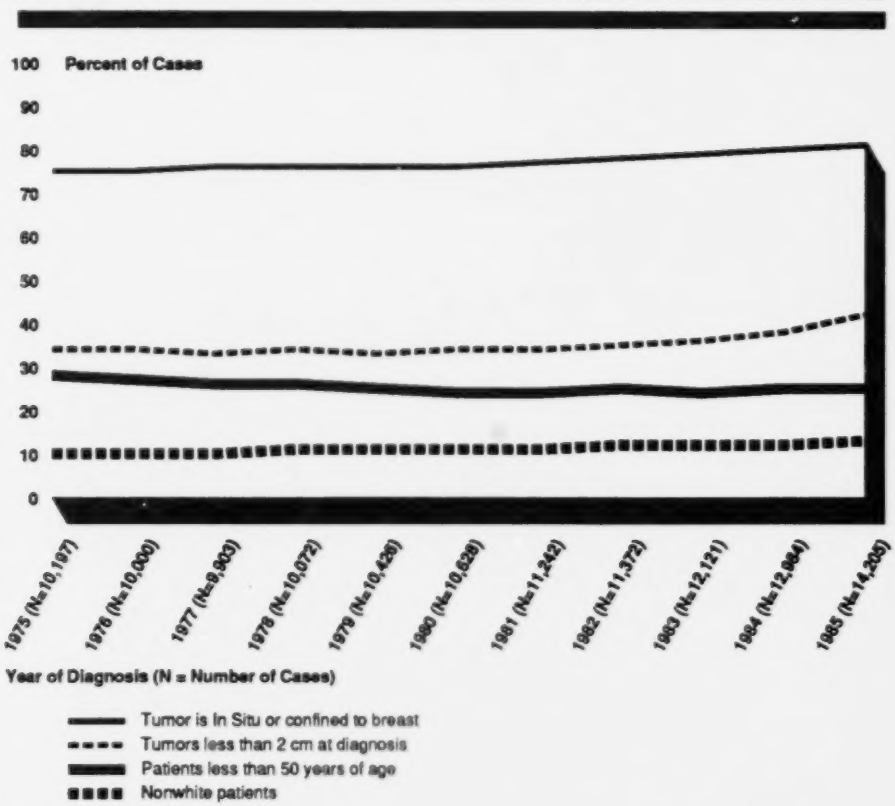
[12]U.S. General Accounting Office, Cancer Treatment 1975-85: The Use of Breakthrough Treatments for Seven Types of Cancer, GAO/PEMD-88-12BR (Washington, D.C.: January 1988).

Treatment Patterns and Survival

Findings

The likelihood of surviving breast cancer for a specified period of time depends on a number of factors. These "prognostic indicators" include characteristics of the patient (age, race, sex) as well as characteristics of the cancer itself (how far it has spread, the types of cells involved, and so on). Figure 3.1 shows, by year of diagnosis and for all breast cancer patients, the characteristics that both are related to survival and have data available from SEER.

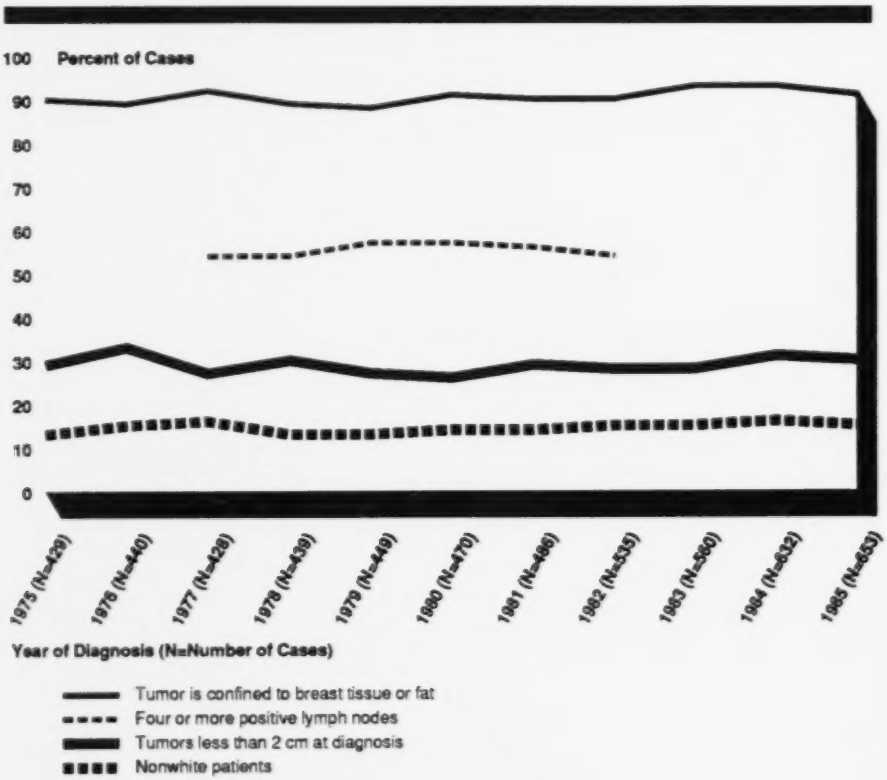
Figure 3.1: Characteristics of All Breast Cancer Patients in SEER 1975-85



As can be seen from this figure, the trend line for each prognostic factor is relatively flat. What this means is that we should expect little, if any, change in patients' survival to result from a shift in the distribution of prognostic factors. This is especially true for patients we selected for our study. Figure 3.2 shows trend lines for this group. If anything, the trend lines show even less change over time than exhibited by the general population of breast cancer patients. (The line for percent of cases

with four or more positive lymph nodes starts in 1977 and ends in 1982 because data on nodal status were not available for any other years.)

Figure 3.2: Characteristics of Premenopausal, Node-Positive, Stage II Breast Cancer Patients in SEER 1975-85



One thing that has changed among the group of patients we selected is the frequency with which adjuvant chemotherapy is administered. As table 3.1 shows, there was a steady increase in the use of chemotherapy from 1975 to 1982.[1] What the table also shows, however, is that 3-, 5-, and 7-year survival rates have remained relatively stable across diagnostic cohorts.

[1]For reasons that are discussed in our January 1988 report on the use of breakthrough treatments, a more precise statement is that there was a decrease in the number of patients not receiving chemotherapy. See U.S. General Accounting Office, Cancer Treatment 1975-85: The Use of Breakthrough Treatments for Seven Types of Cancer, GAO/PEMD-88-12BR (Washington, D.C.: January 1988).

Table 3.1: Premenopausal, Node-Positive, Stage II Breast Cancer Patients: Treatment and Survival Patterns

Year of diagnosis	Percent receiving chemotherapy	Survival rate (.95 confidence interval)[a] 3-year Rate	3-year CI	5-year Rate	5-year CI	7-year Rate	7-year CI
1975	23%	.82	.036	.72	.042	.64	.045
1976	45	.85	.033	.71	.043	.64	.045
1977	46	.83	.036	.71	.042	.64	.045
1978	53	.83	.035	.70	.043	.63	.045
1979	55	.83	.035	.71	.042	.65	.044
1980	62	.86	.031	.77	.038		
1981	66	.83	.033	.72	.040		
1982	72	.84	.031				
1983	69	.85	.030				

[a]The survival rates provided assume complete follow-up only through the end of 1985. That is why the last year for 3-year survival is 1983, for 5-year, 1981, and for 7-year, 1979. The figures in parentheses define the 95-percent confidence intervals for each survival rate estimate. These intervals are constructed by adding the numbers in parentheses to, and subtracting them from, the estimate provided. For example, using the data, we conclude that 95 percent of all possible estimates of the 3-year survival rate for women diagnosed in 1975 would fall between 78.4 (82 − 3.6) and 85.6 (82 + 3.6) percent.

When confidence intervals are constructed for each of the survival rates in table 3.1 (by adding and subtracting the corresponding standard error), there is no instance in which the intervals do not overlap. This means that there is no statistically significant difference between any of the rates. As mentioned in the previous chapter, however, survival rates alone can be misleading, since they measure survival only at specific times rather than along a continuum. Therefore, we also compared the survival of the successive cohorts by using the lifetable method.

The lifetable method compares actual length of survival (not only percentage surviving at specified times) of all cases across groups and provides statistical tests that indicate whether survival is different between the groups. In looking for differences in survival, we first compared the survival experiences of successive diagnostic cohorts (that is, women diagnosed in 1975 with those diagnosed in 1976, those diagnosed in 1976 with those diagnosed in 1977, and so on, through 1984-85). Because of the possibility that there was an incremental improvement in survival that went unnoticed because we only compared proximate cohorts, we also made other comparisons. Among these were

- a comparison of 1975 (the year in which the smallest percentage of patients received adjuvant chemotherapy) with 1982 (the year in which the largest percentage of patients received adjuvant chemotherapy);

- an analysis that combined 1975, 1976, and 1977 into a single cohort and compared that cohort to each of the successive cohorts; and
- an analysis that examined all cohorts simultaneously to see if there was any overall significant difference in survival.

Irrespective of the specific comparisons made, the results were consistent. Specifically, they show that there has been no detectable change in patients' survival since 1975, the year in which adjuvant chemotherapy was proven effective in prolonging the lives of cancer patients. The one exception to this finding is that women diagnosed in 1980 did significantly better than women diagnosed the previous year. Unfortunately, this increase in survival did not hold steady and the 1981 cohort did significantly worse than women whose cancers were discovered in 1980. Reinforcing the finding that the 1980 group is somehow "unique" (and we have no description or explanation of this uniqueness) is a comparison that shows no differences between the 1979 and 1981 groups.

In our final attempt to detect changes in survival, we used proportional hazard models. These models show the extent to which patients' characteristics are related to the probability of dying (relative risk). In our study, the characteristic we were most interested in was the year in which a patient was diagnosed as having breast cancer. The question was whether the probability of death changed from one diagnostic cohort to the next. The results of this analysis are displayed in table 3.2.

Table 3.2: The Relative Risk of Dying for Premenopausal, Node-Positive, Stage II Breast Cancer Patients by Year of Diagnosis

Characteristic	Beta	Relative risk	p-value
Race[a]	.251	1.28	.001
Age at diagnosis	−.013	.99	.003
Tumor size	.358	1.43	.000
Tumor extension	.258	1.29	.000
Year of diagnosis[b]			
1976	.018	1.02	.876
1977	.045	1.05	.693
1978	−.020	.98	.863
1979	−.058	.94	.619
1980	−.338	.71	.009
1981	.016	1.02	.895
1982	−.146	.86	.259
1983	−.126	.88	.333
1984	.011	1.01	.935
1985	.318	1.37	.063

[a]White = 0; nonwhite = 1.

[b]Reference year = 1975.

What table 3.2 shows is that a patient's race and age were both significantly related to the probability of dying (with white patients less likely and younger patients more likely to die). The table also shows that the extent to which a tumor had spread at the time of diagnosis and its size were also related to the probability of death. Finally, with respect to the influence of the year of diagnosis, the results of the proportional hazard models are entirely consistent with those of the lifetable analyses. That is, there is no significant change (p-value less than .05) in the risk of dying from one cohort to the next (once again, with the exception of 1980).

Conclusions

How is this possible? That is, what would explain our consistent finding that there is no observable improvement in breast cancer patients' survival, even though the use of chemotherapy has increased considerably? The most direct, but least likely, explanation is that chemotherapy is not beneficial. The procedure through which chemotherapy was shown to improve survival is accepted as the best method for demonstrating the effectiveness of any therapy. This procedure, known as the randomized clinical trial, provides the strongest evidence that any benefits that are seen should be considered real. This is especially true when more than

one clinical trial shows a therapy to be effective, as with adjuvant chemotherapy for premenopausal breast cancer. Based on the trials conducted, it has been stated conclusively that chemotherapy should have efficacy in the treatment of this group of patients.[2]

A number of more likely reasons exist for why patients may not have realized the benefits of adjuvant chemotherapy. One factor that clearly explains away part of the mystery is that treatment did not change for a considerable number of patients. That is, given that approximately one in five women already received chemotherapy in 1975, there might be little opportunity for improvement among 20 percent of the patients. In addition, it is clear that we should expect no change in survival among the patients who never received chemotherapy. Although this number diminished over time, approximately a third of the patients in the 1985 cohort had not received adjuvant chemotherapy. Among these two groups, we would expect little if any change in survival, since patterns of treatment remained constant.

A second reason why patients have not realized the benefits of chemotherapy may be that the chemotherapy they are receiving is inappropriate. As we discussed in our January 1988 report, SEER data are not sufficiently precise to inform us as to exactly what therapy was used. For example, a treatment advance might be the combination of three specific drugs into a chemotherapeutic regimen. From SEER, however, one can tell only whether or not the patient received chemotherapy. The SEER data are not detailed enough to indicate the exact type of chemotherapeutic regimen administered. As a result, when we say that there has been a twofold-to-threefold increase in the use of chemotherapy for breast cancer patients, this does not necessarily mean that all, some, or any of these women are being treated with the correct combination of drugs, given in proper sequence and at appropriate dosages. That is, the unchanging survival experiences of breast cancer patients, year after year, could be a function of poor implementation of the breakthrough in treatment.

Finally, although it is acknowledged that adjuvant chemotherapy is beneficial in the treatment of premenopausal breast cancer, the question of how large a benefit it provides remains unresolved. Different trials have reported benefits in terms of both disease-free survival and overall survival and have not taken their measurements at a standard time (for

[2]National Institutes of Health, Consensus Development Conference Statement, Adjuvant Chemotherapy for Breast Cancer, 5:12 (1985).

example, one trial may report only 3-year disease-free survival while another may report 9-year overall survival). In addition, even when there is consistency in measurement and reporting, the results often differ. One consequence of the differences is that it is not clear whether our results are surprising or expected. If adjuvant chemotherapy is expected to extend survival for 25 percent of the patients who receive it (as HHS stated in its response to an earlier GAO report), our finding of no detectable improvement in survival is surprising.[3] However, if the true benefit of this therapy extends to only 7-to-10 percent of premenopausal, node-positive breast cancer patients (as HHS currently maintains), it is likely that whatever improvements in survival did occur after 1975 would be too small to detect with the available data and statistical procedures.

Implications

Two of the three competing explanations for why the increased use of adjuvant chemotherapy has not led to detectable improvements in patients' survival have direct, yet different policy implications. If the primary explanation is that many patients are not receiving any adjuvant chemotherapy, efforts to increase the use of this therapy are in order. These efforts would be directed at patients (if their refusal to accept chemotherapy explains their failure to receive the therapy), at physicians (if they do not offer chemotherapy to their patients), or at both groups.

If survival rates have not improved because physicians do not provide the right kind of chemotherapy, some mechanism must be developed to improve the quality of care. More focused training or regulatory efforts are but two strategies for achieving this goal.

However, the third explanation—that the magnitude of the improvement was too small to be detected with all the available data and statistical procedures—does not appear to lend itself to any immediate policy resolution.[4] This is not to suggest that the issue is unimportant, however. The size of the benefit provided by adjuvant chemotherapy is clearly of considerable interest to breast cancer patients and their physicians.

[3]U.S. General Accounting Office, Cancer Patient Survival: What Progress Has Been Made, GAO/PEMD-87-13 (Washington, D.C.: March 1987), p. 114.

[4]One potential resolution would be to expand the number of cases available for analysis. This option, however, would require a considerable expansion of the SEER program.

The point here is that it is essential to determine which of the three explanations is correct and that two of these are potentially susceptible to resolution. We cannot now recommend a policy to adopt because we cannot say which of the three explanations or what combination of them more accurately reflects reality. A variety of strategies exist for making this determination. Unfortunately, each of these strategies has its limitations and none can be assumed to easily provide an answer to the question.

For example, one approach would be to go to patients' case records, determine exactly what type of chemotherapy was or was not given, and then relate the type of therapy to each patient's survival. The problem with this design is twofold: it is expensive, and it depends entirely on case records' providing sufficient detail to allow investigators to identify the therapy that was given.

An alternative strategy for determining the therapy that was provided would be to ask physicians what therapy they gave. This is a less costly design than case record review, but it is open to problems of memory as well as other forms of response bias (for example, physicians might well hesitate to say they did not provide appropriate care).

The most elaborate (and costly) study design would be one in which patients were prospectively followed from the time of diagnosis. By observing exactly how the patients were treated and then tracking their survival, we would have the strongest evidence on what in fact happened and why. Here again, however, there are methodological obstacles. Aside from the costs and time required to conduct a prospective study, there is the issue of physicians' and patients' compliance. If either the patients or their physicians were unwilling to cooperate with a research team, the conclusions of such a study might be methodologically flawed.

These problems present obstacles that must be overcome if a study is to determine conclusively why no improvement in survival is visible.

Recommendation

We recommend that the secretary of the Department of Health and Human Services initiate a study to determine why there has been no detectable improvement in the survival of premenopausal, node-positive breast cancer patients since the advent of chemotherapy in 1975. In light of the potential methodological obstacles that such a study faces, we also suggest that prior to conducting it, the secretary seek expert

advice on the feasibility of conducting the recommended research and the study design most likely to provide valid conclusions.

Agency Comments

The Department of Health and Human Services reviewed a draft of this report. HHS concurred with the recommendations contained in that draft, although the agency suggested including a feasibility analysis prior to the full-scale study. Our current recommendations reflect this suggestion.

HHS summarized its general comments by listing three "major concerns" with our report (see appendix III):

"1.The conclusion, as worded, gives the erroneous impression that no progress against Stage II, premenopausal breast cancer has been made since the advent of adjuvant chemotherapy. The body of the report makes it clear that GAO does believe there has been improvement as evidenced by clinical trials; however, the conclusion as stated gives exactly the opposite impression.

"2.GAO interprets its analysis to show that no increase in survival is detectable by any means. However, the GAO analysis does not have sufficient statistical power to be able to justify this definitive statement.

"3.The Department agrees with GAO that a closer examination of the actual chemotherapy delivered to breast cancer patients would be useful."

In reading through the full text of HHS's comments, we concluded that the "conclusion" mentioned in the first concern is actually the title of the draft report HHS reviewed. We agree that the draft title could have been misinterpreted, so we have changed the title to Breast Cancer: Patients' Survival.

The concern that is most pervasive throughout HHS's comments is described in the second point. In its response to our report, HHS consistently emphasizes the small number of patients included in our study and argues that this number leads to our study's having low statistical power. Furthermore, HHS contends that low statistical power is the major reason that no improvement in survival was detected. That is, the small number of patients makes it likely that whatever the improvement in survival, improvement would not achieve statistical significance. We agree that our findings may result from small sample size. In fact, this point was made in the draft HHS reviewed and remains in this report. However, statistical power is a function of several factors: in addition to sample size, the most important factor in our study is the size of change

in survival one expects (effect size). As either sample size or the size of the expected change decreases, so does the statistical power.

In our analyses, the size of the samples is a given: we included all breast cancer patients from SEER who satisfied NCI's criteria for defining ideal candidates for adjuvant chemotherapy. What is less clear is how large a change in patients' survival should be expected. In its response to a 1987 GAO report, HHS stated that a 25-percent improvement in survival was to be expected for premenopausal breast cancer patients.[5] If this 25-percent estimate of effect size is used, the power of our statistical tests is adequate. However, if HHS's current estimate of 7-to-10-percent is closer to the true effect size, our statistical tests do not have a reasonable probability of detecting that effect. A question remains, however, as to the basis for the change in HHS's estimate of the likely survival benefits from adjuvant chemotherapy.

In that earlier response, HHS also argued that survival rates could be improved significantly "through better application of existing treatments." This position of HHS's supports our conclusion that poor implementation may explain why we did not detect any improvement in patients' survival.

There are, therefore, a number of possible explanations for our findings: the number of patients available for our study was small; the benefits of adjuvant chemotherapy are small; many physicians do not give chemotherapy correctly. HHS, in its responses to this and earlier GAO reports, has agreed with all these factors.

All other comments provided by HHS have been considered and changes have been made in the report as appropriate.

[5]U.S. General Accounting Office, Cancer Patient Survival: What Progress Has Been Made? GAO/PEMD-87-13 (Washington, D.C.: March 1987), p. 114.

Technical Appendix

Measuring Survival Time

The classic problem in survival analysis is that of censoring or right truncation. At issue is what values to assign to the survival times of patients who are still alive at the conclusion of a study. If we simply calculate their survival by time at end minus time of entry, we are equating their survival to that of patients who entered the study at the same time and died near the time that the study ended.

As a solution to the censoring problem, many algorithms add time to anyone who is censored (alive when last seen). Typically, the amount added is half the time in the subsequent interval. For example, any patient who was alive at the end of our study would be given 6 additional months of survival, if we measured survival in years. This method of assigning values to censored cases introduces a bias, because of the natural history of breast cancer and the types of patients we included in our analyses.

Our study was limited to Stage II, premenopausal patients who had had surgery. Among this group of women, it is very unusual for anyone to die (from cancer or other causes) within the first year or two of diagnosis. This means that assigning half an interval to censored data is likely to bias later diagnostic cohorts. For example, consider a patient diagnosed in January 1975 and another patient diagnosed in January 1987. Assume that the probability of death during the first 2 years following diagnosis is small for both patients. Finally, remember that our study ends in January 1988 with the second patient still alive.

Since the study ends with the second patient still alive, her survival time has to be estimated. This estimate measures her survival as 18 months (the 1 year she was measured while alive and the additional half year she gets for being censored). However, the likelihood of her surviving to the end of the second year is great. This means that 24 months (at a minimum) is probably a better estimate.

The problem was aggravated by the fact that our initial censoring date was relatively early (December 31, 1985). We believe that the early censoring date and the bias described above accounted for initial results that showed that women in our last two cohorts had significantly worse survival than other patients. That is, women in 1975, 1976, 1977, and so on had the opportunity to live 2 and 3 years (which most did) whereas those diagnosed in 1985 did not.

To correct for this problem, we extended the censoring date to December 31, 1986. Since we did not have complete follow-up on patients up to

that date, we assumed that any patient who was not recorded as dead was alive at the end date. When this was done, the differences between the 1984 and 1985 cohorts relative to all others disappeared.

Estimating Cohort Effect

In the Cox models, the year of diagnosis was entered into the model in two different ways. One was to record the direct value (for example, 1977, 1978, 1979) of the year in which the patient was diagnosed. We also constructed 11 dummy variables to correspond to each of the 11 annual diagnostic cohorts. It is this latter measurement scheme that is reported in chapter 3.

Also at issue was which cohort should be used as the comparison group for the proportional hazard models. We chose 1975 for the theoretical reason that it was the year in which the advance in treatment was first reported. However, when we combined 1975 and 1976 or combined these two cohorts with 1978 to form a comparison cohort, the results remained unchanged (1980 is the only significantly different cohort).

Statistical Power of the Study Design

In conducting clinical trials, it is advisable to determine the statistical power of the design (the probability that an effect will be detected if one really exists) as early as possible. Among the primary benefits of power estimates is that they allow for modifications in the study design (for example, expanding the number of patients to be enrolled) while such modifications are still easily made. In fact, the utility of power estimates for determining sample size is so well established that tables exist that show the required number of subjects for each desired level of significance and statistical power.[1]

In situations where the analyst is unable to modify the study environment (by increasing either the effect size or the sample size), power estimates serve more to help in the interpretation of study findings than to inform design decisions. The study described by this report is one in which both the effect size and the number of patients included in the analyses were factors beyond the control of the analysts. The utility of any power estimates for this study, therefore, derives primarily from their role in helping in the interpretation of our findings.

[1]For example, L.S. Freedman, "Tables of the Number of Patients Required in Clinical Trials Using the Logrank Test," Statistics in Medicine, 1 (1982), 121-29.

The major finding of our study is that there was no detectable improvement in patient survival over time. If the power of our study is high, this finding would be more accurately stated by omitting the word "detectable" from it. If the power of our study is low, the finding is correctly stated as is and should come as no surprise. (That is, we could not detect any change primarily because the change is difficult to detect with the design we employed.)

Obviously, the alternative conclusions to be drawn from our study, given high or low power, have different implications. A conclusion that there has been no improvement in survival could point to a problem in the way cancer patients are treated. A failure to detect improvement could mean no more than the obvious fact that small effects are difficult to detect. Unfortunately, we could not determine which of these perspectives is more accurate because we could not compute the power of our design.

One reason we could not estimate the power of our study is that there is no agreed-upon estimate of the magnitude of the benefit provided by adjuvant chemotherapy. As we indicate in chapter 3, HHS has itself provided two distinct estimates of effect size, each of which would lead to considerably different estimates of power.

A second reason that we could not estimate power is that the central analyses (the lifetable and proportional hazard comparisons) were performed by making numerous comparisons across the 11 cohorts rather than a simple comparison of one cohort against a second. This presents a number of problems for power computations. One obvious (and insurmountable) one is that we could find no existing algorithm for computing power for an n-way logrank test. An equally vexing dilemma was what comparisons should be included: 1975 against all other years, 1975 and 1976 against all other years, 1975 through 1977 against 1982 through 1985, and so on. Since each of these tests was run, and each would generate different power estimates as a result of different sample sizes, we could generate a wide range of power estimates.

Patient Selection Criteria

In an earlier study on the use of state-of-the-art cancer therapies, we asked NCI to provide us with criteria for selecting the cancer patients who should be the most likely candidates for adjuvant chemotherapy.[1] These criteria were applied to the entire population of breast cancer patients contained in SEER. The patients who satisfied all the criteria were included in the earlier study and also served as the population for the current study.

Patients' Characteristics

The sex of a patient had to be female.

The age of a patient had to be 50 years or less at the time of diagnosis.

The medical history of a patient could not include any previous diagnosis of cancer.

The diagnosis must have been made through some means other than an autopsy.

The diagnosis must have been made in 1975 or later.

The patient must have had surgery.

Tumor Characteristics

The primary site of the tumor was in the breast.

The size of the tumor at the time of diagnosis was less than 5.0 centimeters.

The histology of the tumor was coded as 8140 (adenocarcinoma, Not Otherwise Specified), 8141 (scirrhous adenocarcinoma), or 8500 (infiltrating duct carcinoma), using the International Classification of Diseases, 9th Edition, Oncology.

The tumor could not extend to or beyond the chest wall, and there could be no evidence of metastatic activity to adjacent or distant organs.

The nodal status of the patient had to be positive with only the axillary lymph nodes involved and no involvement of distant lymph nodes.

[1]U.S. General Accounting Office, Cancer Treatment 1975-85: The Use of Breakthrough Treatments for Seven Types of Cancer, GAO/PEMD-88-12BR (Washington, D.C.: January 1988), pp. 1-3.

Comments From the Department of Health and Human Services

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of Inspector General

Washington, D.C. 20201

OCT 18 1988

Ms. Eleanor Chelimsky
Director, Program Evaluation
and Methodology Division
U.S. General Accounting Office
Washington, D.C. 20548

Dear Ms. Chelimsky:

Enclosed are the Department's comments on your draft report, "Breast Cancer: Patients Have Yet to Realize the Benefits of Adjuvant Chemotherapy." The enclosed comments represent the tentative position of the Department and are subject to reevaluation when the final version of this report is received.

The Department appreciates the opportunity to comment on this draft report before its publication.

Sincerely yours,

Richard P. Kusserow
Inspector General

Enclosure

COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES
ON THE GENERAL ACCOUNTING OFFICE'S DRAFT REPORT,
"BREAST CANCER: PATIENTS HAVE YET TO REALIZE THE BENEFITS
OF ADJUVANT CHEMOTHERAPY," SEPTEMBER 1988

General Comments

The Department appreciates the opportunity to comment on the General Accounting Office (GAO) draft report. In its report, the GAO attempts to determine whether an increase in the use of adjuvant chemotherapy has led to a population-wide improvement in survival for women with Stage II breast cancer, under the age of 50, since 1975.

GAO concludes "that despite a considerable increase in the use of chemotherapy since 1975, there has been no detectable increase in survival for those patients who should have benefited most from the advent of this therapy." GAO recommends that the Secretary of the Department of Health and Human Services (DHHS) initiate a study to determine "why there has been no visible improvement in the survival of premenopausal, node-positive, breast cancer patients despite the advent of adjuvant chemotherapy."

The Department agrees with the conclusion drawn in the GAO report that adjuvant chemotherapy clearly prolongs the survival for premenopausal women with Stage II breast cancer. As pointed out by GAO, this survival advantage has been well documented in several, large, randomized clinical studies, and the Department agrees with GAO that "the question of whether (adjuvant) chemotherapy has the potential to extend patient survival has been settled."

The Department also shares GAO's concern that this survival advantage may not be reaching the entire population of Stage II, premenopausal breast cancer patients nationally. Our concerns are two-fold; first, that not all eligible patients are receiving adjuvant chemotherapy, a concern borne out by the GAO analysis which shows that 31 percent of eligible patients did not receive chemotherapy as late as 1983; and second, that patients who are being treated may not be receiving chemotherapy with the intensity (dosage and timing of treatment) needed to achieve the potential survival advantage.

The Department believes, however, that the statistical power of the GAO analysis is not sufficiently strong to allow the sweeping conclusion that no increase in survival benefit can be detected. The major reason for this is that the Surveillance, Epidemiology and End Results (SEER) database contains too few Stage II, premenopausal patients who meet the GAO selection criteria (approximately 400 to 650 per year), to be able to draw a

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definitive conclusion given the magnitude of the survival advantage expected based on clinical trials data (7 to 10 percentage points at 5 years post diagnosis) and given the statistical approach used by GAO. The National Cancer Institute is supporting extensive research to develop therapies which will confer greater survival advantages. However, while this 7 to 10 percent survival improvement represents a significant accomplishment of adjuvant chemotherapy, detecting this difference using the methods employed by GAO would require two to three times as many patients as are available in the SEER database. The Department's analysis indicates that the GAO approach had less than a 50 percent chance of demonstrating an improvement in 5 year survival using the SEER database. This means that there was at least a 50 percent chance that the GAO analysis would miss finding a survival advantage even if one existed.

The Department believes that an incomplete transfer of the adjuvant chemotherapy treatment advance to the community also contributed to GAO not detecting a survival advantage between 1975 and 1983. The fact that only 69 percent of eligible patients received adjuvant chemotherapy in 1983 speaks to this point. On a recent analysis of the SEER database, the Department also found that there were proportionately more patients with four or more positive lymph nodes in the treatment group than in the overall SEER population of Stage II, premenopausal breast cancer patients. This would result in a smaller than expected survival benefit for the treatment group since patients with four or more positive lymph nodes receive a lesser benefit from adjuvant chemotherapy than does the general population of premenopausal, Stage II breast cancer patients (Bonadonna G., Rossi A., Tancini G. et al. (1983) "Adjuvant Chemotherapy in Breast Cancer" (letter) LANCET, 1, 1157). The Department believes that this incomplete transfer of adjuvant chemotherapy to the community may have been a major contributing factor to a lower than expected national survival benefit between 1975 and 1983.

Although the SEER database is the best currently existing resource to have used for the GAO study, it does not contain enough information about patient treatment to definitively answer questions about the impact of particular treatments on survival and about patterns of care. The SEER database does not capture information about the nature of treatment (single agent versus combination chemotherapy), the dosages given, or the length of treatment. It is, therefore, not possible to determine whether adjuvant therapy is being given in the community using the same methods which improve survival in clinical trials.

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The main conclusion of the GAO draft report is stated in the title, "Breast Cancer: Patients Have Yet to Realize the Benefits of Adjuvant Chemotherapy". The Department believes that this statement is uninformative and possibly misleading. If this conclusion means that the breast cancer patients who actually received adjuvant chemotherapy showed no survival benefit, we disagree; GAO did not provide evidence to support this assertion. If it means that there has been no possibly discernible impact on the whole Stage II, premenopausal population, we also disagree. As stated above, the GAO analysis does not have sufficient statistical power to prove that a survival benefit from adjuvant chemotherapy has not occurred nationally. The Department suggests that a more appropriate title for the GAO report might be, "Adjuvant Chemotherapy for Breast Cancer: Is a Survival Benefit Detectable in the National Statistics?" The use of this alternative title could prevent a misunderstanding about the fact that adjuvant therapy is an effective method of treatment.

In conclusion, the Department has three major concerns with the GAO report:

1. The conclusion, as worded, gives the erroneous impression that no progress against Stage II, premenopausal breast cancer has been made since the advent of adjuvant chemotherapy. The body of the report makes it clear that GAO does believe there has been improvement as evidenced by clinical trials; however, the conclusion as stated gives exactly the opposite impression.

2. GAO interprets its analysis to show that no increase in survival is detectable by any means. However, the GAO analysis does not have sufficient statistical power to be able to justify this definitive statement.

3. The Department agrees with GAO that a closer examination of the actual chemotherapy delivered to breast cancer patients would be useful.

GAO Recommendation

GAO recommends that the Secretary of the Department of Health and Human Services (HHS) initiate a study to determine why there has been no detectable improvement in the survival of premenopausal, node-positive, breast cancer patients since the advent of adjuvant chemotherapy in 1975. GAO also recommends that prior to initiation of such a study, the Secretary convene and seek the advice of an advisory committee as to the design most likely to provide valid conclusions. This committee should include representatives from the cancer research community, practicing oncologists, physicians other than oncologists who have a role in

cancer patient management and women who have been treated for breast cancer. Care should be exercised in selecting the participants to ensure that the major professional societies are also represented. This is to increase the likelihood of cooperation by all relevant parties with any study endorsed by this group.

Department Response

The Department agrees with the GAO recommendation, but not with the way it is stated. As mentioned in the General Comments section, and described in more detail in the Technical Comments section, the GAO analysis does not have the statistical power to state that there has been no improvement in survival for Stage II, premenopausal breast cancer patients. The number of women in the SEER database, in the category selected by GAO, is too small (400 to 650 per year) to be able to detect a change in survival of the size predicted from the clinical trials literature using the GAO approach. It is, therefore, not appropriate for GAO to recommend a study to determine why there has been no apparent survival improvement, but rather whether adjuvant therapy for breast cancer has been successfully transferred from clinical trials to clinical practice.

A patterns of care study of the delivery of adjuvant therapy for breast cancer, not just in Stage II premenopausal women, would be important and could provide valuable insights to aid the transfer of clinical trials advances to clinical practice. The Department agrees that an advisory panel should be convened prior to the initiation of a study, not only to advise on study design, but to assess the feasibility of successfully conducting such a study. The availability and adequacy of patient records are the major factors which influence the feasibility of a patterns of care study. Any study design chosen will require the complete availability of patient records to provide detailed information about chemotherapy agents used, dosage, frequency, and length of treatment. In a clinical trial, such data collection and monitoring is standard and agreed upon, in advance, by the patient and physician. For a patterns of care study of the delivery of therapy which is principally done in individual physicians' offices, physicians would have to agree to keep records in greater detail than is customary. Furthermore, access to records of patients not participating in a clinical trial would be essential and would require an unprecedented level of cooperation and openness on the part of physicians and their patients. Should the advisory committee determine that a patterns of care study is feasible, it would be advisable to conduct a pilot study prior to the full scale effort to be certain that the necessary information can be obtained.

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Additionally, a patterns of care study would require a significant commitment of personnel, equipment, and financial resources over a several year period.

Technical Comments

Title Page

The title of the report, Breast Cancer: Patients Have Yet to Realize the Benefits of Adjuvant Chemotherapy asserts a conclusion that cannot be supported by the report itself, does not accurately reflect the contents, and could suggest to the public that adjuvant chemotherapy is not an effective method of treatment. GAO specifically states that it does not attack the positive findings for adjuvant chemotherapy in clinical trials, but the title clearly states patients have yet to realize the benefits of adjuvant chemotherapy. GAO failed to find a survival improvement reflected in national statistics for Stage II, premenopausal patients, but the size of the sample and the treatment effect which could be expected based on a careful analysis of the clinical trials data made the likelihood of finding this improvement less than 50 percent.

The report notes that 31 percent of the premenopausal women who have Stage II breast cancer, a stage for which chemotherapy is indicated, did not receive adjuvant therapy in 1983. The title of the report could inadvertently lead to a decrease in the percentage of women who receive adjuvant chemotherapy as it leaves the mistaken impression that this treatment, which has well known side effects, is useless.

Now page 2.

Page ES-1, Paragraph 1

The report opens with the assertion that the Nation spends billions of dollars on new medical technologies. Since the passage of the National Cancer Act in 1971, the National Cancer Institute has spent a total of $4.55 billion on all forms of cancer treatment research out of its total appropriation of $14.3 billion during this time period. The largest expenditures have been for basic research and have led to an unprecedented understanding of the nature of cancer.

Now page 3.

Page ES-4, Table 1

* Now pages 2 and 3.

GAO's multivariate analyses on pages 3-8 include cases through 1985, yet Table 1 stops at 1983. If 1985 cases are part of the GAO analysis, they should also be included in Table 1.

Page 6

Now page 3.

Page ES-5, Paragraph 1

GAO describes several plausible reasons that might contribute to the failure to detect benefits of adjuvant chemotherapy in national survival statistics. It omits the fact that many physicians who are hesitant to prescribe chemotherapy do so only for their patients with the worst prognoses; large primary tumor, more than four positive lymph nodes, aggressive histology, etc. The Department's analysis of the SEER data supports this assertion and shows that there were proportionately more patients with four or more positive lymph nodes in the treatment group than in the whole SEER Stage II, premenopausal population. This would result in a smaller survival benefit for the treatment group since patients with four or more positive lymph nodes receive a lesser benefit from adjuvant chemotherapy than does the overall population of premenopausal, node-positive breast cancer patients (Bonadonna G., Rossi A., Tancini G. et al. (1983) "Adjuvant Chemotherapy in Breast Cancer" (letter) LANCET, 1, 1157).

In addition to these factors, GAO should note that the small number of breast cancer patients in the SEER database who fit the criteria for its study (428 to 653 each year), and the modest size of the expected gain (7.3 to 10.8 percentage points in clinical trials) result in a serious lack of power in the statistical analyses. This makes it highly improbable that a national benefit could be detected even if the women who were given adjuvant chemotherapy did have their lives extended. It should be noted that clinical trials can detect this survival difference enrolling a smaller number of patients because a survival difference is being sought between two populations, 100 percent of whom receive treatment on one arm of the study and zero percent who are treated on the other arm. In the SEER data analyzed by GAO, the comparison is made between the 23 to 71 percent who received treatment over the time period of the study, a change in treatment status of only 48 percent. This makes larger numbers of patients necessary to detect an evolving survival advantage.

Now pages 7 and 9.

Page TC-3, Abbreviations and Page 1-3

L-PAM is an acronym for L-phenylalanine mustard, not for L-phenylalanine (which is a non-cytotoxic amino acid).

Now page 8.

Page 1-1

Reference is made to the focus of the GAO report being "... the advance made when it was discovered that chemotherapy administered following surgery (adjuvant chemotherapy) improves the survival chances of premenopausal breast cancer patients." The group referred to in the report is actually women with

Page 7

evidence of spread of the breast cancer into axillary (underarm) lymph nodes (node-positive), not all premenopausal breast cancer patients. In addition, the term adjuvant chemotherapy should be more clearly defined. It refers only to chemotherapy given to women with no detectable disease following definitive local therapy (surgery or radiotherapy) in an attempt to eradicate undetectable, microscopic cancer cells which may remain in the body and does not include chemotherapy given to patients who have evidence of metastatic disease.

Now page 8

Page 1-2

The chronology of cancer drug development is inaccurate. The first use of antitumor agents in humans was in 1943 when alkylating agents were first used at Yale to treat patients with leukemia and Hodgkin's disease. The first curative chemotherapy was reported in the late 1950's when methotrexate was used in the treatment of metastatic choriocarcinoma. Curative combination chemotherapy of many of the leukemias and lymphomas was developed in the 1960's.

Now page 9

Page 1-3

The GAO report states that "... drugs showed little promise in treating carcinomas ..." until the mid-1970's. This is incorrect. By the mid-1970's, chemotherapy had been shown to have significant antitumor activity in choriocarcinoma, breast cancer, ovarian carcinoma, and small cell carcinoma of the lung. The impact of effective chemotherapy for these carcinomas is further magnified when the young median age of patients with some of these cancers is taken into account. Although more effective chemotherapeutic regimens have since been developed for these carcinomas, the contributions of these early regimens in terms of tumor response and overall survival should not be underestimated.

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Page 1-4

Clinical trials of adjuvant chemotherapy in premenopausal, node-positive breast cancer patients have consistently shown a 30 to 50 percent reduction in relapse rate at 5 years. The 75 percent reduction referred to in the GAO report was reported in only one study and is not considered a standard estimate of the effectiveness of adjuvant chemotherapy in this population. Further, this reduction in relapse rate does not translate to an equivalent change in the probability of survival.

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Page 1-6, Ref. 12

NATO, when used in this context, stands for Nolvadex (the trade name for tamoxifen) Adjuvant Trial Organization.

Page 8

Now page 12.

Page 2-2, Paragraph 2

The wording of the fourth line could be construed to mean that SEER contacts all patients directly for follow-up. The SEER data base is developed from hospital records, death records, and sometimes letters to the patient's physician in order to obtain the most recent follow-up information. However, SEER registries almost never contact patients directly.

Contrary to the statement in the report, the SEER database does not contain information on "... how the patient was treated." SEER data does not contain information on the nature of the treatment (i.e. single agent or combination chemotherapy), the duration of the therapy (i.e. single course versus six or more cycles of therapy), and the dose-intensity (i.e. amount of drug given over a unit period of time), all of which have been shown to significantly influence the outcome of patients treated with adjuvant chemotherapy. SEER does not include information on whether patients receive therapy equivalent to that shown to be effective in clinical trials. These limitations of SEER are described only near the end of the report, on pages 3-12 and 3-13, but should be mentioned in the Objectives, Scope, and Methodology portion of the report as well.

Now page 24.

GAO reports that "... SEER provides information on patient characteristics (age, race and sex) that are useful for creating homogeneous strata of patients for analysis." GAO is correct that SEER reports the listed characteristics. However, a number of factors which could significantly influence response to adjuvant chemotherapy are not reported in SEER, including important variables such as estrogen receptor status. In assessing a population's response to adjuvant chemotherapy, it is important that prognostic features be known in order to be able to predict the magnitude of the expected survival benefit.

Now page 12.

Page 2-2, Paragraph 3

The text should make clear that 3-year follow-up data was not available for the patients entered into the GAO study who were diagnosed in 1984 and 1985. The problems created by the censoring methods used to deal with this are discussed in the Technical Comments on Page I-1.

Now page 30.

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Page 2-5, Paragraph 1

GAO states that "This disease is diagnosed in approximately 120,000 women... the second most prevalent form of cancer..." This statement follows one which limits the discussion to only premenopausal women. The 120,000 represents all new cases of breast cancer diagnosed in 1985, not just the premenopausal subset which constitutes approximately 22 percent of the total.

Page 9

Breast cancer has the second highest incidence rate after lung cancer. However, this does not imply that it is the "second most prevalent" form of cancer. Prevalence, or cumulative incidence up to the patient's present age, means the number of people currently alive who have a history of a particular cancer. Because of the much longer survival for breast cancer than for lung cancer, there are many more persons alive today with a history of breast cancer than of lung cancer (Feldman A.R., Kessler L., Myers M., and Naughton M.D. (1986) "The Prevalence of Cancer: Estimates Based on the Connecticut Tumor Registry" NEW ENGLAND JOURNAL OF MEDICINE, 315, 1394-1397).

Now page 14.

Page 2-5, Paragraph 1 to 2-6, Paragraph 1

GAO should succinctly state the selection criteria for these analyses. This information, as well as the number of women per year included in the group studied, should be included in the text. Figure 3.2 shows that the number of women in the study cohort for 1975 was 429, rising in 1983 to 653, with intermediate size cohorts in the intervening years. The small number of cases on which this analysis is based should be clearly stated in the report, not just in a figure.

The report says that "cancer patients under the age of 50" were included in the study group. However, the SEER data provided by the National Cancer Institute at GAO's request, included females aged 50 and under, a somewhat larger group. The above sentence should be revised to say, "patients 50 and under" if this was the population of women studied. The description of the study cohort should include the histologies of the breast cancers which were included for analysis. This information was omitted from the description of the methodology. Page I-1 mentions that only surgically treated patients were included, but this fact is not stated in The Selection of Patients and it is not made clear whether that selection was indeed made. It would aid the interpretation of this study if the selection criteria were presented in tabular form indicating how many cases each criterion included as compared to the total SEER node positive, premenopausal breast cancer population.

Now page 30.

Now page 17.

Page 2-11

GAO overstates the power of the statistics which they employ in their analysis in concluding "If the coefficients did not achieve significance, we concluded that any observed change was probably due to chance." If the tests achieve significance, then the effect has a low probability (usually 5 percent) of being a spurious finding. However, the opposite is not true. There can be many reasons why, when an effect is real, the tests do not achieve statistical significance. Some of the reasons include an

Page 10

insufficient number of cases, the proportion of cases affected is small, the effect being measured is small, the power is weak, and/or the model is inappropriate.

Now page 20.

Page 3-5

Although SEER shows that there has been a steady increase in the use of chemotherapy from 1975 to 1982, SEER does not include information on the number of cycles of chemotherapy, the combination of agents used or the dosage, all factors which have been shown in clinical investigations to exert a major influence on the effectiveness of the treatment.

Now page 22.

Page 3-7

The statement is made here and elsewhere "... there has been no detectable change in patient survival since 1975..." The Department believes that this wording is misleading. If GAO wishes to summarize the results of its analysis more accurately, the statement should read, "In our analysis of the SEER data, GAO was unable to detect a significant improvement in survival in this group of breast cancer patients." Similar changes should be made on Page 3-9, Paragraph 2 and Page 3-10, Line 1.

Now page 23.

The first step in conducting a study such as that undertaken by GAO would be to determine, given the available data, the probability of being able to detect a survival difference between groups if one existed. This concept is termed the power of the study. To calculate power, an estimate of survival, assuming maximal benefit of adjuvant chemotherapy, must be provided. National Cancer Institute scientists using the same information as that available to GAO have made the following calculations. Based on review of the papers by Moon et al. (Jones S.E., Moon T.E., Bonadonna G., Valagussa P., Rivkin S., Buzdar A., Montague, E., and Powles T. (1987) "Comparison of Different Trials of Adjuvant Chemotherapy in Stage II Breast Cancer Using a Natural History Data Base" AMERICAN JOURNAL OF CLINICAL ONCOLOGY, 10(5) 387-395; and Moon T.E., Jones S.E., Bonadonna G., Valagussa P., Powles T., Buzdar A., and Montague E. (1987) "Development and Use of a Natural History Data Base of Breast Cancer Studies" AMERICAN JOURNAL OF CLINICAL ONCOLOGY, 10(5) 396-403), the Department estimates that the 5 year survival for women on clinical trials under 50 who have positive nodes and tumor size less than 5 centimeters is 75.5 percent for those receiving adjuvant chemotherapy compared to 64.7 percent for those who do not. For a particular diagnosis-year in the SEER data only a percentage of the patients had adjuvant chemotherapy. Thus, for any given year we can calculate the expected 5-year survival as: (.755) (percent receiving adjuvant chemotherapy) + (.647) (percent not receiving adjuvant chemotherapy).

Page 11

In the SEER database, there are several chemotherapy usage categories: 1) no chemotherapy; 2) chemotherapy received; 3) chemotherapy recommended - unknown if received; 4) unknown if chemotherapy received. If we assume that everyone who had chemotherapy recommended (group 3) received it, then Table 1 shows the expected 5 year survival for each diagnosis year from 1975-1985.

Table 1

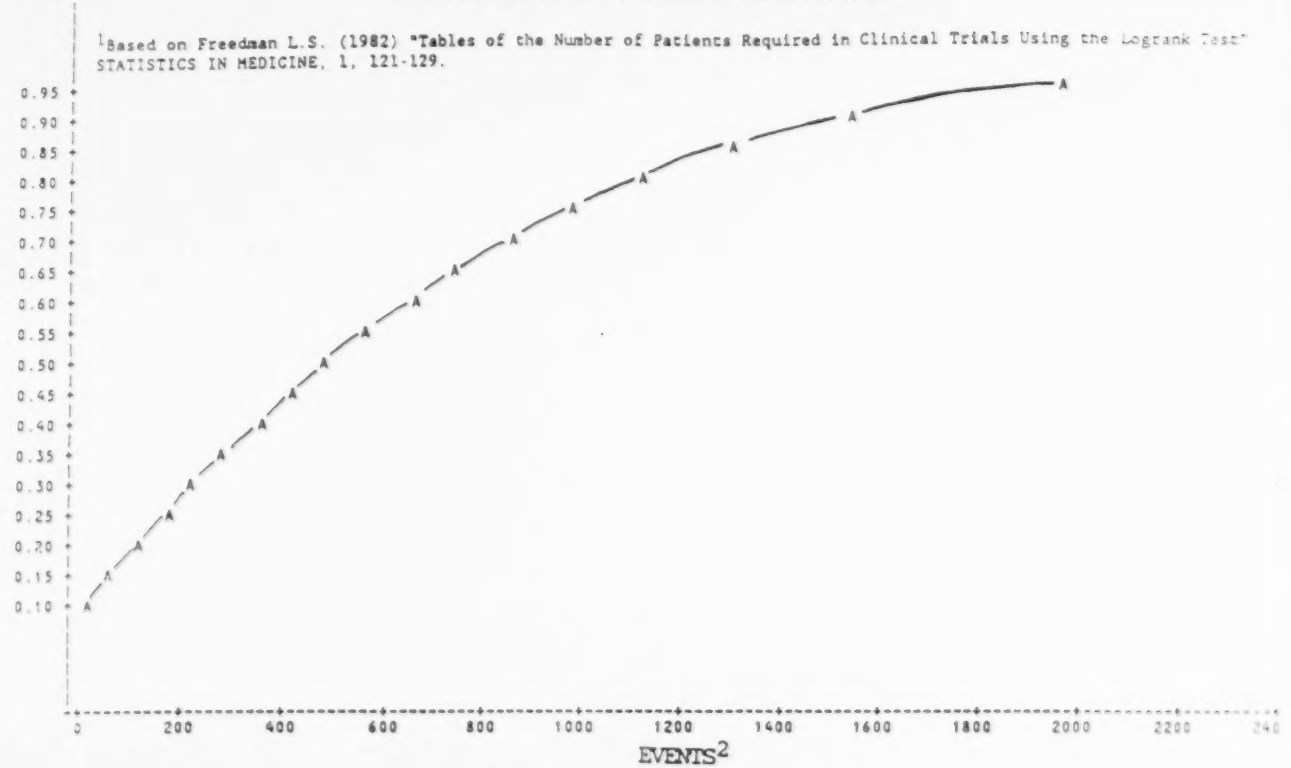
DX YEAR	% RECEIVED CHEMO	% CHEMO RECOMMENDED, UNK. IF RECEIVED	TOTAL % CHEMO	5 YR EXPECTED SURVIVAL
1975	19.6	3.3	22.9	.672
1976	33.8	11.6	45.4	.696
1977	34.0	11.9	45.9	.697
1978	45.9	6.8	52.7	.704
1979	45.2	9.8	55.0	.706
1980	48.8	12.5	61.3	.713
1981	54.0	12.1	66.1	.718
1982	55.5	15.9	71.4	.724
1983	54.1	14.6	68.7	.721
1984	45.7	21.0	66.7	.719
1985	47.9	15.0	62.9	.715

Thus, a maximum difference of 5.2 percentage points in 5 year survival (1975 to 1982) would be expected based on the survival benefit of adjuvant chemotherapy demonstrated in clinical trials.

Power calculations were performed using the results of Freedman (Freedman L.S. (1982) "Tables of the Number of Patients Required in Clinical Trials Using the Logrank Test" STATISTICS IN MEDICINE, 1, 121-129) for comparisons of two survival curves with the logrank test. Figures 1 and 2 show power versus number of events (deaths) needed (in both groups together) to detect a change in 5 year survival from .672 to .71 and .72, respectively. (Note that the x-axis in Figures 1 and 2 are on different scales.) In both curves we assume a one sided Type I error rate of .05. If we assume that there are about 300 events available for analysis (which is approximately the number of deaths available from SEER for each pair of years being compared) then the power to detect a change from .672 to .71 is between 35 and 40 percent, and the power to detect a change from .672 to .72 is only 50 percent. This level of power is unacceptable because the chance of missing the expected improvement in survival due to chemotherapy is 50 percent or more.

FIGURE 1

POWER TO DETECT A DIFFERENCE IN FIVE YEAR SURVIVAL FROM .67 TO .71 (HAZARD RATIO = 1.16) AS A FUNCTION OF THE NUMBER OF EVENTS (DEATHS) USING A ONE SIDED .05 LEVEL LOGRANK TEST[1]

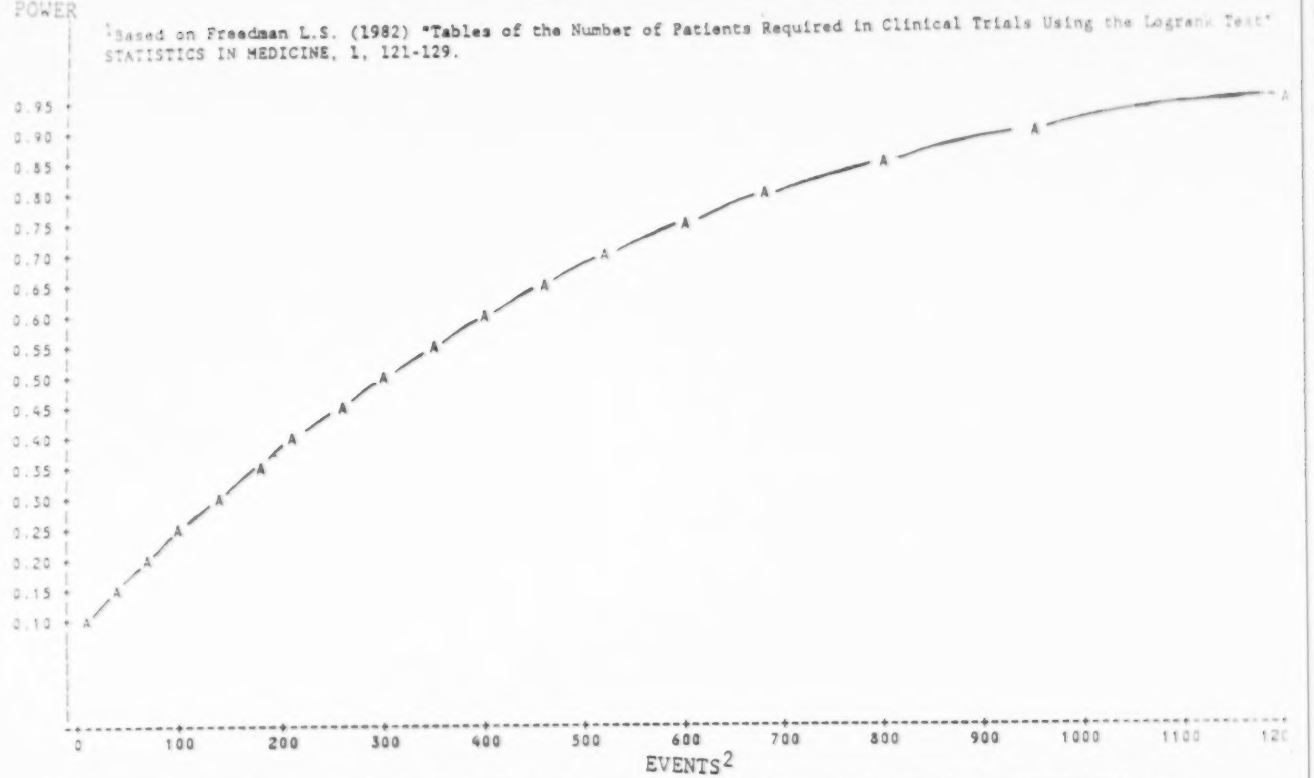


[1]Based on Freedman L.S. (1982) "Tables of the Number of Patients Required in Clinical Trials Using the Logrank Test" STATISTICS IN MEDICINE, 1, 121-129.

[2]The number of events represents the deaths in both groups combined. Follow-up only extends through the follow-up period of the shorter of the two groups (eg. for diagnosis year 1975 and 1980 with follow-up through 1986, only deaths within 7 years count as events.)

FIGURE 2

POWER TO DETECT A DIFFERENCE IN FIVE YEAR SURVIVAL FROM .67 TO .72
(HAZARD RATIO = 1.21) AS A FUNCTION OF THE NUMBER OF EVENTS (DEATHS)
USING A ONE SIDED .05 LEVEL LOGRANK TEST[1]



[2]The number of events represents the deaths in both groups combined. Follow-up only extends through the follow-up period of the shorter of the two groups (eg. for diagnosis year 1975 and 1980 with follow-up through 1986, only deaths within 7 years count as events.)

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Looking again at Figures 1 and 2, we would need 1,119 events to detect a change from .672 to .71 with 80 percent power, and we would need 685 events to detect a change from .672 to .72 with 80 percent power.

The Department's analysis described above uses data from selected trials reviewed and analyzed by Moon and colleagues. A comprehensive review of adjuvant trials undertaken by R. Peto and colleagues, "The Effects of Adjuvant Tamoxifen and of Cytotoxic Therapy on Mortality in Early Breast Cancer: An Overview of 70 Randomized Trials among 30,000 Women," suggests that five year survival rises from 65.7 percent to 73.0 percent due to adjuvant chemotherapy, a smaller difference than that suggested by the Moon et al. review. If this smaller, but statistically significant effect, is indeed the expected benefit, then the GAO analysis would have even less of a chance of detecting it.

Now page 22.

Page 3-7, Paragraph 2

Now page 23.

Analysis of the SEER data using multivariate survival modeling, of which the Cox proportional hazard approach used by GAO is one example, is quite appropriate for the basic aims of the GAO study. The GAO model, shown on page 3-8, is related to the pairwise year comparisons used in the GAO's second analysis. As noted above, the pairwise analysis has insufficient power to test the basic hypotheses of the study. Adjusting for covariates could improve power if there is a relationship between the year-independent variables, the covariates, and survival. However, as GAO points out, there is little change over time in the covariates.

Now page 23.

Page 3-9, Paragraph 2

The GAO statement that it can find no observable improvement in breast cancer patient survival should be amended to specify that it cannot find evidence of improvement for the subset of women included in its analysis and that its analysis had less than a 50 percent chance of detecting an improvement of the magnitude expected from clinical trials. The current statement ignores the improvement seen in large clinical trials.

See pages 24-25.

Page 3-10

The footnote on the bottom of the page is a key point that should be emphasized in the text: there are not enough data and the sample size is not large enough to detect the differences expected based on a comprehensive review of the reported clinical trials.

Page 13

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Page 3-11, Paragraph 2

It is not clear whether the range of 10 to 30 percent survival improvement refers to relative or absolute percent change in survival. There is little evidence to suggest that the survival improvement conferred by chemotherapy is larger than 10 percent absolute difference at 5 years.

The Department believes that many cancer patients for whom adjuvant chemotherapy has been shown to improve survival in clinical trials do not receive it or do not receive the regimens most likely to be effective. The Department has multiple programs in place to disseminate information to the public and to physicians about cancer prevention, diagnosis, and treatment. Efforts to provide treatment information to physicians are described in the recent response to the GAO report "Cancer Treatment: The National Cancer Institute's Role in Encouraging Doctors to Use Breakthroughs."

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Page 3-12, Paragraph 3 and continuing on page 3-13

GAO expresses a concern that the Department may be promoting therapies which, though effective in clinical trials, do not change patient outcomes when used in clinical practice. There is no inherent reason why adjuvant breast cancer therapies which are effective in clinical trials, cannot be delivered correctly in clinical practice. The critical concern is that practicing physicians may modify effective therapies thereby rendering them less than optimally effective.

Now page 26.

Page 3-14

Third paragraph (first line), the word "most" should be "must".

Now page 27.

Page 3-15

The Department believes that before attempting to design a patterns of care study, an advisory committee should consider whether such a study is feasible, taking into account the obstacles enumerated in the General Comments section. The Department believes that if an advisory committee recommends that such a study be done, it should be preceded by a pilot study to assure feasibility prior to undertaking a full-scale patterns of care study. The panel convened should consider the advisability and feasibility of a broader study of the delivery of cancer therapy, extending beyond breast cancer.

Page 14

Now pages 30-32.

Page I-1 to I-3

There are many problems and inconsistencies in this section. To summarize: 1) most life table methodologies do not add the one-half interval of survival, but rather assume everyone survived one-half of the interval in which they were censored; 2) the example is inappropriate; 3) changing the study cut-off date and assuming that everyone not reported dead, but lost to follow-up, was alive in December 1986 is not justified. The Department would use a conservative approach and employ December 1985 as the study cut-off rather than December 1986 because follow-up is fairly complete by this date, i.e. almost all patients are either dead or known to be alive on December 31, 1985. GAO's approach could bias its results in either direction.

Now page 31.

Page I-3 Paragraphs 2 and 3

The two different ways of coding the year variable (the direct value or 1 through 11) will produce identical findings. These are not really separate analyses. More importantly, the analysis done in this manner is not the most appropriate. If year is used as a proxy for chemotherapy, then this analysis implies a monotonic functional relationship between survival and year. This was not the case in the SEER data, as shown in Table 1, and this violates the assumption of proportional hazards.

An alternative is to use the percent receiving chemotherapy each diagnosis calendar year as a continuous independent variable. Everyone diagnosed in a particular calendar year would have an identical value of the covariate. This alternative would be a more appropriate way of approaching the data and, in the departmental analyses, does yield results suggesting a survival benefit from chemotherapy. Assumptions about follow-up, and the use of covariates, however, do affect the results of this analysis. There are several ways to approach the SEER data, and the GAO analysis did not utilize methods most likely to demonstrate the expected survival benefit.

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Page I-5

The calculations in the last column of Table I.1 imply a decision rule that says if at least one of the two pairwise comparisons is significant, then one would conclude a significant benefit of chemotherapy in the general population. However, this is not the decision rule used in the report, since the 1975 versus 1980 comparison is significant.

The power estimates reported in Table I.1 (Appendix I), according to the footnote, make the assumption that no women received chemotherapy in 1975 and 1976 and that 100 percent were treated with chemotherapy post 1976. Using these assumptions, GAO

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overestimates the power to detect survival differences. The Department notes that more appropriate calculations indicate a lower power to detect differences of a magnitude that can be expected based on clinical trials data.

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